Citation:

Folsom AR, Demissie Z. Fish intake, marine omega-3 fatty acids, and mortality in a cohort of postmenopausal women. *Am J Epidemiol.* 2004, Nov 15; 160(10): 1005-1010.

PubMed ID: 15522857

Study Design:

Cohort study.

Class:

B - Click here for explanation of classification scheme.

Research Design and Implementation Rating:

NEUTRAL: See Research Design and Implementation Criteria Checklist below.

Research Purpose:

To assess whether fish or marine omega-3 fatty acid intake is inversely associated with major causes of death in a cohort of women with generally low coronary heart disease mortality.

Inclusion Criteria:

The Iowa Women's Health Study cohort comprises of 41,836 women, aged 55 to 69 years, recruited via a baseline questionnaire mailed in 1986.

Exclusion Criteria:

None described.

Description of Study Protocol:

Design

Cohort study.

Study Protocol

- Baseline risk factors and medical history described in detail in an earlier publication
- Baseline dietary intake assessed by using a 127-item food frequency questionnaire
    - Four fish and seafood questions asked about frequency of intake of
        - Dark-meat fish such as mackerel, salmon, sardines, bluefish, or swordfish [84g to 140g (three to five ounces)]
        - Canned tuna [84g to 112g (three to four ounces)]
        - Other fish [84g to 140g (three to five ounces)]
        - Shrimp, lobster or scallops as a main dish [98g (3.5 ounces)]

- Frequency categories ranged from "never or less than once per month" to "six or more per day"
- In 1987, 1989, 1992 and 1997 cancer incidence and most deaths identified
  - By annual linkage of cohort identifiers to
    - Iowa state-wide cancer incidence and death records
    - Questionnaires mailed to the cohort
    - National Death Index
  - By ICD-9 and ICD-10 codes: Cardiovascular [*International Classification of Diseases*, Ninth Revision (ICD-9) codes 390 to 459; *International Classification of Diseases*, Tenth Revision (ICD-10 codes I00 to I99), coronary heart disease (ICD-9 codes 410 to 414, 429.2; ICD-10 codes I20 to I25, I51.6), stroke (ICD-9 codes 430 to 438; ICD-10 codes I60 to I69, G45), and cancer (ICD-9 codes 140 to 239; ICD-10 codes C00 to D48].

Statistical Analysis

- Quintiles to analyze our single 1986 assessment of total fish and seafood intake and of marine omega-3 intake
- Analysis of covariance to examine the relation of fish quintiles to other risk factors
- Poisson regression or proportional hazards models to compute relative risks and 95% confidence intervals (95% CI) of death, adjusted for age and energy and covariates previously reported to be associated with total and cardiovascular mortality in this cohort.

Data Collection Summary:

Timing of Measurements

- Baseline questionnaire about risk factors, medical history and food intake (1986)
- Cancer incidence and most deaths identified by annual linkage of cohort identifiers to:
  - Iowa state-wide cancer incidence and death records and by questionnaires mailed to the cohort in 1987, 1989, 1992 and 1997
  - Follow-up surveys of the National Death Index
- Cause of death as assigned by state health departments, as follows:
  - Cardiovascular
    - International Classification of Diseases, Ninth Revision (ICD-9) codes 390 to 459
    - International Classification of Diseases, Tenth Revision (ICD-10) codes I00 to I99, coronary heart disease (ICD-9 codes 410 to 414, 429.2; ICD-10 codes I20 to I25, I51.6), stroke (ICD-9 codes 430 to 438; ICD-10 codes I60 to I69, G45),
  - Cancer (ICD-9 codes 140 to 239; ICD-10 codes C00 to D48)

Dependent Variables

- Mortality measured by person-years
- Cardiovascular disease mortality measured by number of events
- Coronary heart disease mortality measured by number of events
- Stroke mortality measured by number of events
- Cancer mortality measured by number of events
- Other mortality measured by number of events
- Breast cancer incidence measured by number of events

Independent Variables

Total fish and seafood intake during 1986.

Description of Actual Data Sample:

- *Initial N:* 41,836 women
- *Age:* 55 to 69

Anthropometrics

Distribution of Baseline Risk Factors in Relation to Baseline Fish Intake Among Participants Initially Free of Cancer and Cardiovascular Disease, Iowa Women's Health Study, 1986

	Frequency of Fish Intake Per Week (Servings, Approximate Quintiles)					P for Trend
	<0.5	0.5 to <1.0	1.0 to 1.5	>1.5 to <2.5	≥2.5	
Prevalence (%)						
Age more than 62 years	50	49	48	46	45	<0.0001
Education, high school or higher	69	64	60	56	54	<0.0001
Low level of physical activity	57	54	47	43	38	<0.0001
Alcohol nonconsumer	68	62	53	45	47	<0.0001
Current smoker	16	15	15	16	14	0.004
First livebirth at age 30 years or more	6	6	6	6	5	0.17
Current estrogen user	10	11	11	13	13	<0.0001
Vitamin user	30	30	33	35	37	<0.0001
Body mass index more than 30kg/m^2	23	22	22	22	25	<0.0001
Waist/hip ratio more than 0.85	42	42	40	40	39	0.06
Diabetes	5	5	5	5	6	0.63
Hypertension	33	33	34	36	37	<0.0001
Mean						
Energy intake (kcal per day)	1,607	1,673	1,797	1,888	1,973	<0.0001

Whole-grain intake (servings per week)	9.6	10.2	11.1	11.9	13.5	<0.0001
Fruit and vegetables intake (servings per week)	34.9	37.3	42.6	47.4	55.2	<0.0001
Red meat intake (servings per week)	5.7	5.9	6.0	6.0	5.8	<0.0001
Keys score*	17.9	18.2	18.5	18.7	19.1	<0.0001
Cholesterol (mg per day)	231	247	271	290	318	<0.0001
Saturated fat intake (g per day)	22.9	23.3	24.3	24.9	24.6	<0.0001
Alpha-linolenic intake (g per day)	0.96	1.01	1.09	1.14	1.21	<0.0001

* Reflects the serum-cholesterol-raising capacity of the diet.

Summary of Results:

Relative Risks of Total and Cause-specific Deaths and Incident Breast Cancer in Relation to Baseline Fish Intake Among Participants Initially Free of Cancer and Cardiovascular Disease, Iowa Women's Health Study, 1986 to 2000

	Frequency of Fish Intake Per Week (Servings, Approximate Quintiles)					**P for Trend**
	<0.5	**0.5 to <1.0**	**1.0 to 1.5**	**>1.5 to <2.5**	**≥2.5**	
Mortality person-years	50,038	77,410	174,852	48,325	92,341	
Total mortality (number of events)	606	833	1848	476	890	
RR1*	1.0	0.90	0.88	0.83	0.82	0.003
95% CI†	Reference	0.8, 1.00	0.81, 0.97	0.73, 0.94	0.74, 0.91	
RR2‡	1.0	0.99	0.97	0.93	0.93	0.15
95% CI	Reference	0.88, 1.11	0.88, 1.07	0.83, 1.05	0.83, 1.05	

Cardiovascular disease mortality (number of events)	220	304	590	144	331	
RR1*	1.0	0.91	0.79	0.71	0.87	0.005
95% CI	Reference	0.77, 1.09	0.68, 0.93	0.57, 0.88	0.73, 1.03	
RR2‡	1.0	1.03	0.86	0.79	0.95	0.11
95% CI	Reference	0.85, 1.23	0.73, 1.02	0.63, 0.99	0.78, 1.15	
Coronary heart disease mortality (number of events)	121	181	337	80	203	
RR1*	1.0	0.99	0.82	0.71	0.95	0.02
95% CI	Reference	0.78, 1.24	0.66, 1.01	0.53, 0.94	0.76, 1.20	
RR2‡	1.0	1.11	0.86	0.75	1.04	0.31
95% CI	Reference	0.87, 1.42	0.69, 1.08	0.55, 1.03	0.80, 1.34	
Stroke mortality (number of events)	38	69	115	26	65	
RR1*	1.0	1.21	0.91	0.75	1.01	0.23
95% CI	Reference	0.82, 1.81	0.63, 1.33	0.45, 1.24	0.68, 1.53	
RR2‡	1.0	1.30	0.95	0.90	1.06	0.65
95% CI	Reference	0.86, 1.96	0.64, 1.41	0.53, 1.53	0.67, 1.67	
Cancer mortality (number of events)	227	305	779	201	328	
RR1*	1.0	0.88	0.99	0.93	0.80	0.01
95% CI	Reference	0.74, 1.04	0.86, 1.15	0.77, 1.13	0.67, 0.95	
RR2‡	1.0	0.97	1.10	1.03	0.91	0.61
95% CI	Reference	0.81, 1.16	0.93, 1.29	0.84, 1.27	0.75, 1.11	
Other mortality (number of events)	159	224	479	131	231	

RR1*	1.0	0.92	0.86	0.85	0.78	0.18
95% CI	Reference	0.75, 1.13	0.72, 1.03	0.67, 1.07	0.64, 0.96	
RR2‡	1.0	0.95	0.93	0.96	0.93	0.61
95% CI	Reference	0.77, 1.18	0.76, 1.12	0.75, 1.23	0.74, 1.17	
Breast cancer incidence (number of events)	210	320	762	219	374	
Person-years	47,369	72,809	164,196	45,162	86,143	
RR1*	1.0	1.04	1.01	1.04	1.01	0.99
95% CI	Reference	0.87, 1.24	0.87, 1.19	0.86, 1.26	0.85, 1.20	
RR2‡	1.0	0.96	0.91	0.97	0.92	0.49
95% CI	Reference	0.80, 1.16	0.77, 1.08	0.79, 1.19	0.76, 1.12	

* Relative risk (RR) adjusted for age (continuous) and energy intake (quintiles).

† CI (confidence interval).

‡ Relative risk adjusted for age, energy intake, educational level (less than high school, high school or more than high school), physical activity level (low, medium or high), alcohol consumption (0, less than 4.0g or 4.0g per day or more), smoking status (current, former or never), pack-years of cigarette smoking (continuous), age at first livebirth (nullipara, less than 30 years, or 30 years or more), estrogen use (current, former or never), vitamin use (yes, no or unknown), body mass index (quintiles), waist/hip ratio (quintiles), diabetes (yes or no), hypertension (yes, no or unknown), intake of whole grains, fruit and vegetables, red meat, cholesterol and saturated fat (all in quintiles).

Relative Risks of Total Mortality and Breast Cancer Incidence in Relation to Baseline Quintiles of Estimated Omega-3 Fatty Acids from Fish Among Participants Initially Free of Cancer or Cardiovascular Disease, Iowa Women's Health Study, 1986 to 2000

	Quintile of Omega-3 Fatty Acid Intake (g per Day)					**P for Trend**
	≤0.05	**0.06–0.10**	**0.11–0.16**	**0.17–0.26**	**≥0.27**	
Mean intake	0.02	0.08	0.13	0.21	0.47	
Total mortality						
Person-years	86,882	82,248	96,107	89,342	88,387	

Number of events	960	835	1,014	959	885	
RR1*	1.0	0.94	0.97	0.96	0.91	0.40
95% CI†	Reference	0.85, 1.03	0.89, 1.06	0.88, 1.05	0.83, 1.00	
RR2‡	1.0	0.98	1.01	1.04	0.96	0.79
95% CI	Reference	0.89, 1.08	0.91, 1.10	0.94, 1.14	0.86, 1.06	
Breast cancer incidence						
Person-years	81,929	77,150	90,043	83,798	82,759	
No. of events	384	340	437	364	360	
RR1*	1.0	1.04	1.01	1.02	1.01	0.99
95% CI	Reference	0.90, 1.20	0.88, 1.16	0.89, 1.18	0.87, 1.17	
RR2‡	1.0	0.99	0.94	0.92	0.91	0.19
95% CI	Reference	0.84, 1.15	0.81, 1.09	0.79, 1.08	0.77, 1.08	

* Relative risk (RR) adjusted for age (continuous) and energy intake (quintiles).

† CI, confidence interval.

‡ Relative risk adjusted for age, energy intake, educational level (less than high school, high school or more than high school), physical activity level (low, medium or high), alcohol consumption (zero, less than 4.0g or 4.0g per day or more), smoking status (current, former or never), pack-years of cigarette smoking (continuous), age at first livebirth (nullipara, less than 30 years or 30 years or more), estrogen use (current, former or never), vitamin use (yes, no or unknown), body mass index (quintiles), waist/hip ratio (quintiles), diabetes (yes or no), hypertension (yes, no or unknown), intake of whole grains, fruit and vegetables, red meat, cholesterol and saturated fat (all in quintiles).

Other Findings

A secondary analysis (not shown in the tables): The association of total mortality with fish intake for women who at baseline were free of cancer but reported a history of myocardial infarction, angina or other heart disease:

- 1,069 deaths, 42,095 person-years
- A modest, inverse association between fish intake and total mortality in these women
- The age- and energy-adjusted relative risks of total mortality across quintiles of fish intake were
    - 1.00, 1.09 (95% CI: 0.88, 1.36),
    - 0.95 (95% CI: 0.78, 1.15)
    - 0.83 (95% CI: 0.64, 1.07)
    - 0.88 (95% CI: 0.71, 1.10)
- P for trend: 0.14
- This association was eliminated with multivariate adjustment (P for trend = 0.88)

- Estimated marine omega-3 fatty acid intake and specific groups of fish or seafood also were unrelated to total mortality (P for trend, 0.85) in women with a history of heart disease.

Plant-derived alpha-linolenic acid was modestly inversely associated with total mortality (relative risks across tertiles = 1.0, 0.95, 0.85; P for trend = 0.01, adjusted for all covariates).

Author Conclusion:

In conclusion, in this sample of post-menopausal women, greater fish intake was weakly, but not independently, associated with a reduced rate of death. There was also no independent association of fish intake with coronary heart disease or stroke mortality. These findings do not argue against recommending fish as part of a healthy diet, as other evidence suggests benefit. Nevertheless, we could not verify that fish and marine omega-3 fatty acid intake had independent health benefits in these post-menopausal women.

Reviewer Comments:

There are several major flaws in this study.

- *The authors did not query the use of fish-oil supplements by the participants. They cite minimal use by participants of the WHS as justification. However, at least 30% of the subjects in each quintile of this study reported vitamin use. Omission of this data may have lead to underestimation of fish-derived fatty acid intake and consequent null findings.*
- *The EPA and DHA content of livestock and chickens (and chicken eggs) was not addressed by the authors. Iowans may have greater accessibility to free-range livestock and chickens than residents of other states. This could be another source of measurement error.*
- *The authors did not account for medications that may have influenced subsequent death from cardiac disease*
- *The questionnaire used to define fish-derived omega-3 fatty acids was not validated prior to use*
- *A single self-reported assessment of intake is likely inadequate to capture meaningful consumption data. Dietary habits could have been misrepresented or changed in subsequent years during the study.*

Research Design and Implementation Criteria Checklist: Primary Research

Relevance Questions		
1.	Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies)	N/A
2.	Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	Yes
3.	Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to nutrition or dietetics practice?	Yes

4.	Is the intervention or procedure feasible? (NA for some epidemiological studies)	N/A

Validity Questions

1.	**Was the research question clearly stated?**	Yes
1.1.	Was (were) the specific intervention(s) or procedure(s) [independent variable(s)] identified?	Yes
1.2.	Was (were) the outcome(s) [dependent variable(s)] clearly indicated?	Yes
1.3.	Were the target population and setting specified?	Yes
2.	**Was the selection of study subjects/patients free from bias?**	Yes
2.1.	Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	N/A
2.2.	Were criteria applied equally to all study groups?	Yes
2.3.	Were health, demographics, and other characteristics of subjects described?	Yes
2.4.	Were the subjects/patients a representative sample of the relevant population?	???
3.	**Were study groups comparable?**	Yes
3.1.	Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	N/A
3.2.	Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	Yes
3.3.	Were concurrent controls used? (Concurrent preferred over historical controls.)	N/A
3.4.	If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	Yes
3.5.	If case control or cross-sectional study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	N/A
3.6.	If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	N/A
4.	**Was method of handling withdrawals described?**	No

4.1.	Were follow-up methods described and the same for all groups?	???
4.2.	Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	???
4.3.	Were all enrolled subjects/patients (in the original sample) accounted for?	???
4.4.	Were reasons for withdrawals similar across groups?	???
4.5.	If diagnostic test, was decision to perform reference test not dependent on results of test under study?	N/A
5.	**Was blinding used to prevent introduction of bias?**	No
5.1.	In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	N/A
5.2.	Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	N/A
5.3.	In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	No
5.4.	In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	N/A
5.5.	In diagnostic study, were test results blinded to patient history and other test results?	N/A
6.	**Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were interveningfactors described?**	No
6.1.	In RCT or other intervention trial, were protocols described for all regimens studied?	N/A
6.2.	In observational study, were interventions, study settings, and clinicians/provider described?	No
6.3.	Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	No
6.4.	Was the amount of exposure and, if relevant, subject/patient compliance measured?	Yes
6.5.	Were co-interventions (e.g., ancillary treatments, other therapies) described?	No
6.6.	Were extra or unplanned treatments described?	No
6.7.	Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	Yes
6.8.	In diagnostic study, were details of test administration and replication sufficient?	N/A

7.	**Were outcomes clearly defined and the measurements valid and reliable?**		No
	7.1.	Were primary and secondary endpoints described and relevant to the question?	Yes
	7.2.	Were nutrition measures appropriate to question and outcomes of concern?	Yes
	7.3.	Was the period of follow-up long enough for important outcome(s) to occur?	Yes
	7.4.	Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	No
	7.5.	Was the measurement of effect at an appropriate level of precision?	Yes
	7.6.	Were other factors accounted for (measured) that could affect outcomes?	No
	7.7.	Were the measurements conducted consistently across groups?	Yes
8.	**Was the statistical analysis appropriate for the study design and type of outcome indicators?**		Yes
	8.1.	Were statistical analyses adequately described and the results reported appropriately?	Yes
	8.2.	Were correct statistical tests used and assumptions of test not violated?	Yes
	8.3.	Were statistics reported with levels of significance and/or confidence intervals?	Yes
	8.4.	Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	N/A
	8.5.	Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	Yes
	8.6.	Was clinical significance as well as statistical significance reported?	N/A
	8.7.	If negative findings, was a power calculation reported to address type 2 error?	No
9.	**Are conclusions supported by results with biases and limitations taken into consideration?**		Yes
	9.1.	Is there a discussion of findings?	Yes
	9.2.	Are biases and study limitations identified and discussed?	Yes
10.	**Is bias due to study's funding or sponsorship unlikely?**		Yes
	10.1.	Were sources of funding and investigators' affiliations described?	Yes
	10.2.	Was the study free from apparent conflict of interest?	Yes